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Process optimization in biologics final drug product manufacturing

Abstract

Process optimization, in essence, consists of evaluating a process workflow for improvement purposes by effectively utilizing available resources. This paper aims to focus on the Biologics Final Drug Product (FDP) manufacturing process with regard to exploring the nuances of the standard methodology and gauge how it can be more streamlined to achieve more efficient manufacturing outcomes. This is achieved by performing a comprehensive exploration of FDP Manufacturing industry strategies alluding to deviations and management of rejects, risk level analysis, as well as automated systems & reducing human intervention to attain a holistic understanding for varied elements of FDP manufacturing and identify potential improvements to drive more optimal results with the same set of resources in this rapidly evolving market.

Keywords: final drug product, biologics, process optimization, deviation, secondary packaging, automated process, ancillary kit

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Abbreviations: DS, drug substance; DP, drug product; FDP, final drug product; FDA, food and drug administration; FMEA, failure mode effects analysis; QbD, quality by design; AI, artificial intelligence; API, active pharmaceutical ingredient

Introduction

In recent times, the terms pharmaceuticals and small molecules have been replaced by terms like biotech and cell culture therapies. There may be a lack of clarity as to what Biotech really is, and how it is different from the pharmaceutical industry.[1,2] This paper serves to provide a high-level overview on the ways with which Biologics manufacturing, specifically final drug product manufacturing may be made more efficient. First what is the definition of biologics?

In simple terms, biologics is the driving force behind biotechnology.[3] It is the hot topic of today and is hypothesized to have a lasting appeal in the years to come on the pharmaceutical landscape, largely due to its potential for targeted therapies, adaptability to patient needs, as well as the evolved regulatory framework supporting innovation at lower costs.[2] In biologics, parts of living organisms (cells, proteins, tissues, antibodies) are utilized in creating therapies that target a specific ailment1. The ability to hit specific targets goes a long way in allowing for more effective treatments (with fewer side effects) as opposed to small molecule drugs synthesized from chemical compounds which tend to shoot for several targets at a time, thereby increasing side effects as well as the chances of off-target toxicity.[4]

Upstream & downstream manufacturing

So, now that we've established the basis of biologics and its role in the biological drug development process, the next step is to understand the various branches that fall under the biologics umbrella, namely upstream and downstream manufacturing, as seen in Figure 1. Upstream includes Drug Substance Manufacturing, wherein the active pharmaceutical ingredient (API) is produced through cell line development.[5,6] Downstream includes Drug Product Manufacturing, which produces the final formulation (API + excipients) that gets filled in the appropriate containers, and Final Drug Product Manufacturing, wherein final sterile packaging of the finished product occurs prior to distribution to patients.[7]

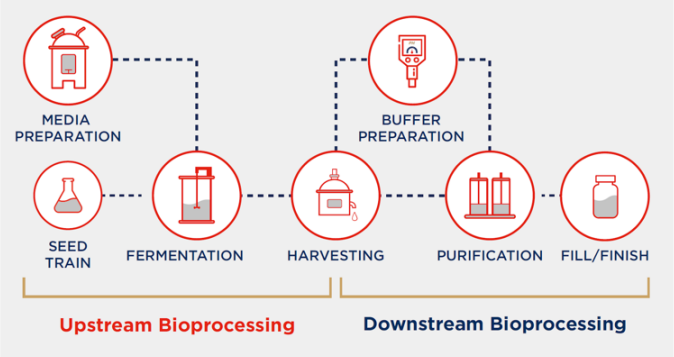

Figure 1 Overview of biologics manufacturing, i.e., Bioprocessing.

Process optimization in biologics FDP manufacturing -a synopsis

This paper aims to focus on the Final Drug Product (FDP) manufacturing process and explore the nuances of the typical process and gauge how it can be more streamlined to achieve more efficient manufacturing outcomes. As mentioned previously, it is the second process in downstream manufacturing that succeeds Drug Product (DP) manufacturing.[8] By the end of DP manufacturing, the product has been formulated, filled, stoppered, and sealed.[9] However, an important thing to understand about biologics drugs is that the majority need to be administered via injection or infusion due to the complex nature of the drugs, which poses the risk of breakdown leading to a lack of absorption if consumed orally.[10,11] Additionally, biologics pride themselves on targeted delivery with higher potency dosage requirements; thus, direct administration under the skin (injection) or into the bloodstream (infusion) proves to be the safest and most effective approach. As you can imagine, these methods of administration are slightly more complex than your typical oral dosage and demand specific devices to facilitate their delivery. Thus, FDP manufacturing takes the container/device prefilled with the final drug product and facilitates the secondary packaging for distribution, which consists of labelling and assembly (i.e., blisters or unit cartons). It also includes packaging of ancillary components to support the administration of the drug, such as alcohol swabs, syringes, bandages,

needles, and infusion sets. Like any complex process, a continual goal in FDP manufacturing is to strive for continuous improvement, or optimizing processes for maximum efficiency.

Process optimization is really very simple to understand - it refers to evaluating the current process workflow to identify opportunities for improvement and implementation of changes that will achieve continuous improvement objectives by making the most of the available resources.[12] Of course, that also includes waste reduction. In the subsequent sections, this paper aims to explore various areas that may serve as serious potential for making the FDP process more streamlined.

Strategies in process optimization

Deviations and management of rejects

In the Biotech world, deviations might derail the standard manufacturing process and prompt investigations due to outcomes that fail to meet the established industry standards.[13,14] Even a seemingly ideal process can sometimes fail, and the deviation investigations are utilized by Biotech companies to keep their processes in check.[13] Nonetheless, an investigation elicits several discussions to assess the quality of the product as a result of the issue and may result in product/material discard. For example, if investigator conducts a review of the FDP manufacturing process, where they identify a lack of an established segregation protocol (that allows only the affected product/materials to be kept aside, thereby allowing the unaffected product/materials to continue through manufacturing), absence of in-process testing (such as visual inspections and quality reviews which serve as control mechanisms to confirm the quality of the product), as well as a defined rework process (which would prompt rejection of entire lot(s) rather than only the affected lot).[15] Such a scenario would inhibit the investigation from being able to narrow the scope of the impacted product down to just the affected batch and may lead to increased waste (fewer batches salvaged) as well as additional resources to prove the quality of the products due to the failure mode. This is a poor example of process optimization. Rather, considering the opposite scenario wherein the investigator identifies that the FDP manufacturing process where the deviation occurred has been able to distinguish between the impacted product/material to be set aside due to a robust segregation protocol, which has been further reviewed by the shop floor Quality team and observations have been documented in the respective system. Furthermore, the identified rejects are disassembled, inspected, reassembled, tested & QA review/approved per defined process. As one might envision, this is a great example of a seamless process wherein a deviation investigation would not result in excessive product discard due to a well-defined scope that is limited to the impacted product/material.[16, 17]

Risk level analysis

Based on the aforementioned discussions around packaging, it is safe to assume that primary packaging, due to its direct product contact, is subject to higher considerations due to its need to protect and maintain product integrity.[18,19] Thus, it enjoys more rigorous regulatory requirements in comparison to secondary packaging.[20,21] In fact, the Food and Drug Administration (FDA), which is a critical authority in the Biotech industry, has separate guidelines for each type of packaging, which are exceedingly more strict for primary packaging.[20] In a nutshell, primary packaging, due to its direct contact with a drug product, is assessed for compatibility, protection from light and oxidation, and contamination prevention.[22] Secondary packaging, on the other hand, serves primarily as an additional cushion during transport, with an added layer providing further protection to the drug product; due to which this type of packaging is assessed for several of the same criteria as primary packaging but with far less stringent guidelines.[18] Examples of both packaging types are illustrated in Figure 2. You may be wondering why this is relevant to this discussion. Well, the relevance becomes much clearer once you become familiar with the difference between the packaging types; if the Biotech Gatekeeper defines each packaging type and assesses them per their level of contact with the drug product, then Biotech companies may also do the same to save considerable time and resources. However, many companies tend to have the same (or similar) risk scale for different kinds of packaging, which ultimately leads to increased expenses.[23]

Figure 2 Overview of product packaging.

(A) Primary packaging (B) Secondary packaging.

But see, there's usually a sound rationale behind this uniform approach. The FDA does encourage the usage of robust risk analysis tools such as Failure Mode Effects Analysis (FMEA) and Quality by Design (QbD) for drug development and manufacturing; due to which many companies are geared towards the utilization of those tools with the intent of applying a thorough approach across several manufacturing processes, including packaging requirements.[24] However, tools such as FMEA and QbD are standardized methodologies that take into consideration the quality of the drug product from the get go and ensure its maintenance throughout the process while identifying design defects and focusing on how they can be addressed.[13] The upside is these approaches demonstrate well-thought-out efforts that show anyone watching the careful considerations that go into developing a drug product for patient consumption. The downside is that such over-engineered solutions can sometimes result in an overkill of sorts, particularly in the context of packaging.[23] So, an effective process optimization strategy in this instance (and any similar instances) would be to consider the nuances in every process that distinguish one system from another and evaluate the need to generalize or differentiate the details when analysing for

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risk. Such an approach goes a long way in providing an equally high integrity of the product while reducing non-essential expenses.[25,26]

Automated systems & reducing human intervention

Automation, or the use of technology to reduce manual processes, can look different in every industry. In retail, it can mean self-checkout machines.[27] In energy, it can mean smart grids. In biotech, it means anything from automated cell culture systems to automated pipettes.[28] In FDP Manufacturing specifically, since it is the tail end of the biologics manufacturing process, a conveyor system to allow the movement of the drug product device and/or materials is integrated with a robust robotic presence to carry out tasks like component transfer, insertion of labels/brochures, and even quality checks.[27] Now, it is understood that a fully automated process is a considerable achievement as far as process optimization goes due to its efficiency, consistency, scalability, and commitment to quality/compliance.[26] Even with a substantial monetary investment, the long-term benefits are well worth the hassle.[29]

That said, why is this a topic worth discussing regarding optimization? It seems to be obvious that automated systems are the way to go, right? Remember in the initial discussion where the complexity of biologics drugs was established? This complexity, to reiterate, is of an unparalleled rank.[30] So naturally, the precision and level of control drive up the cost of production to a degree that accounts for a significant chunk of funds, which therefore cannot be utilized in the investment for transitioning into state-of-the-art automation.[31] Additionally, legacy systems that have been in place since the dawn of time may incorporate outdated infrastructure that is not compatible with today's tech-savvy world, making it difficult for many companies to upgrade these systems to this trendy talk-of-the-town tech.[32-34]

So let's dive into a few strategies worth exploring for Biotech companies on a budget to still alleviate FOMO and maximize their Automation capabilities. Firstly, the concept of partial automation can be promising potential wherein companies focus on critical processes that would benefit the most from minimized human intervention. For example, investing in automated inspection systems during Packaging & Assembly operations may aid in the identification of product/material defects, thereby eliminating the human errors associated with missed defect detection. Another option may be to consider a modular approach to invest in automation systems step by step, which helps planning of incremental investments per the available funds. For example, a company may decide to break down their Packaging process into three (3) modules for stepwise automation: incorporation of an automated conveyor for efficient transportation of the product/materials, investing in Robotic Arms to aid in the repetitive tasks such as ancillary kit placement, and integrating Quality inspection systems to ensure Quality Control. This approach is designed for the independent development of each module, allowing companies to remain agile to meet market demands while testing the Automation waters to meet their Lean objectives.[35,36]

A glimpse into the future

The preceding pages explore process optimization in various areas of biologics final drug product manufacturing, so it felt right to conclude with speculation regarding its future.

Biologics is a new and emerging landscape with tremendous potential, as is another new and emerging area-Artificial Intelligence (AI). The intersection between the two domains is inevitable and has significant growth capabilities. In the last section, we discussed automated systems and their role in upscaling FDP Manufacturing processes. Although the goal of several biotech companies may be to achieve fully automated capabilities in the near future, there remains a difference between systems driven by AI versus technology-driven systems in how they contribute to biologics manufacturing. A fully automated universe relies heavily on predefined algorithms that drive machinery to achieve the desired outcome. Thus, once programmed, the system will do its job seamlessly until it hits a snag, i.e., an unforeseen disruption in the normal process or environmental changes unfamiliar to it based on its pre-programmed intellect. That's when human intervention will play a critical role. An AI universe, on the other hand, consists of the functionality possessed by an automated system with a built-in brain that can quickly adapt to changing environments and learn from existing data.[35] It can assess metrics to suggest improvements in analysing defects, update packaging production schedules based on changing demand-the list goes on. However, this world is still light years away from materializing; so while looking to the future is beneficial, it's more beneficial to focus on the resources available currently and utilize them efficiently to achieve a streamlined process that is deviation-proof, right-sized, and self-driven with minimal need for human input. Process optimization is not some grand vision, but is a fundamental mind-set that allows us to achieve efficient outcomes through daily tasks. Just remember, consistent atomic moves lead to macro wins!

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Conflicts of interest

The authors declare that there is no conflicts of interest.

References

1. Coulter B. *The potential of biologics- what does the future hold?* FDA. 2024.
2. *Biological product innovation and competition*. USA FDA. 2024.
3. Morrow T, Felcone LH. Defining the difference: what makes biologics unique. *Biotechnol Healthc*. 2004;1(4):24–29.
4. Walker N. Biologics: driving force in pharma. *PharmaS Almanac*. 2024.
5. Dorey E. Forces driving the evolution of biologics into biosimilars and biobetters. *Pharma J*. 2024.
6. Coulter B. Cell line development for biologics. 2024.
7. Dubey A. Cell line development -biologics development from early phase to IND during the drug discovery process. *Drug Target Review*. 2019;1.
8. Understanding final drug product manufacturing. *Drug Target Review*. 2021.
9. Kivimaa H. Pharmaceutical manufacturing process: steps and regulations. *Katana*. 2024.
10. *Manufacturing scale-up of drugs and biologics*. NIH. 2024.
11. Eder M. Drug substance vs. drug product: key differences explained. *Single Use Support*. 2023.
12. FDA. Q11 development and manufacture of drug substances. U.S. department of health and human services. 2012:1–36.

13. *Complete guide to pre-clinical drug product manufacturing*. Agno Pharmaceuticals. 2023.
14. Common causes of deviations in the pharmaceutical industry. CfPIE. 2022.
15. FDA. Guidance for industry on container closure systems for packaging human drugs and biologics. 1999.
16. FDA. Packaging and labeling. 2015:1–38.
17. Bouton G. Guidelines for pharmaceutical packaging and labeling. *GCB Solutions*. 2020.
18. Primary packaging vs secondary packaging. UPM Pharmaceuticals. 2022.
19. WHO. Annex 9: Guidelines on packaging for pharmaceutical products. 2009:1–38.
20. Margolis D. Advancing structured benefit-risk assessment in FDA review. *Duke Margolis Center for Health Policy*. 2017:1–10.
21. Draft guidance on use-related risk analysis for drugs, biological products, and combination products. FDA. 2024.
22. Parker M, Smith R, Johnson, L. Risk management strategies in pharmaceutical manufacturing: balancing quality and cost. *J Pharma Sci.* 2022;111(5):1234–1245.
23. Fully automated cell biology workflows. *Automata*. 2024.
24. Automated cell culture systems. *HighRes Biosolutions*. 2024.
25. Molecular Devices. Automated cell culture system. 2023.
26. Automated cell culture expert group. NIH card. 2022.
27. Biologics development: five steps to a robust cell line development process. *Drug Development Delivery*. 2023.
28. Types of laboratory automation systems. HighRes Biosolutions. 2024.
29. CME automation systems. New modular automation system PACE. 2024.
30. Zymergen sells modular automation system for drug discovery. 2022.
31. AI in biopharma: use cases and considerations. AlphaSense. 2024.
32. Manzano T, Whitford W. Artificial intelligence in the biopharmaceutical industry: treacherous or transformative? *Bioprocess International*. 2024.
33. Stucky T. AI to Impact clinical trials and manufacturing in life sciences. *Pharmaceutical Executive*. 2023.
34. The role of AI in biologics manufacturing: current trends and future directions. UPM Pharmaceuticals. 2024.
35. Primary vs. secondary packaging in pharma industry. GMP Insiders. 2022.
36. Liquid pumps for bio pharmaceutical application. Bio-pharmaceutical. Thomas pumps. 2024.

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